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(21) International Application Number: PCT/US93/05619 (22) International Filing Date: 14 June 1993 (14.06.93) (30) Priority data: 07/901,342 19 June 1992 (19.06.92) US (71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). (72) Inventors: HUGHES, Timothy, John ; 9681 Tulip Tree Court, Loveland, OH 45140 (US). GUNDAL, Christine, Marie ; 8676 Summer Wind Bay, Woodbury, MN 55125 (US). (74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45202 (US).		(81) Designated States: AU, CA, FI, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: TOPICAL AROMATIC RELEASING COMPOSITIONS (57) Abstract The present invention relates to topical aromatic releasing compositions containing one or more volatile aromatic compounds selected from the group consisting of menthol, camphor and eucalyptus oil and derivatives thereof and mixtures thereof. In further embodiments, these compositions are also useful for providing relief from nasal symptoms.		

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TOPICAL AROMATIC RELEASING COMPOSITIONS

TECHNICAL FIELD

5 The present invention relates to topical aromatic decongestant pharmaceutical compositions for nasal administration. In particular, it relates to such topical aromatic compositions containing one or more volatile aromatic compounds selected from the group consisting of menthol, camphor and eucalyptus oil and derivatives thereof and mixtures thereof along with a pharmaceutically-acceptable saline solution carrier.

BACKGROUND OF THE INVENTION

10 The common cold, although not usually a serious illness, is a highly prevalent, discomforting and annoying infliction. The term "common cold" is applied to minor respiratory illnesses caused by a variety of different respiratory viruses. While rhinoviruses are the major known cause of common colds, accounting for approximately 15 30 percent of colds in adults, viruses in several other groups are also important. While immune responses occur, and infection with some respiratory tract viruses therefore could be prevented by a vaccine, development of a polytypic vaccine to cover all possible agents is impractical. Thus, the problem of controlling acute upper 20 respiratory disease presents complex challenges, and the long-desired discovery of a single cure for the common cold is an unrealistic expectation.

With rhinovirus infection, symptoms of nasal discharge, nasal congestion, and sneezing usually commence on the first day of 25 illness and progress to maximum severity by the second or third day. The costs of treating colds with over-the-counter medications in the United States is estimated at an annual cost of over 1.5 billion dollars. The direct costs of treatment in outpatient clinics is estimated at almost four billion dollars. Indirect costs, based on 30 the amount of loss in wages because of restricted activity are substantially higher.

At present, only symptomatic treatment is available for the common cold; the majority of these drugs are taken orally. Exemplary prior art oral compositions for treatment of nasal and 35

other cold, flu, allergy and sinus symptoms and the discomfort, pain, fever and general malaise associated therewith generally contain an analgesic (aspirin or acetaminophen) and one or more antihistamines, decongestants, cough suppressants, antitussives and expectorants. Other specific pharmaceutical actives for nasal symptoms (e.g., congestion) generally contain either oxymetazoline or phenylephrine. These actives are generally delivered topically to the nasal mucosa via a nasal spray. For individuals with certain medical conditions such as heart disease, hypertension, diabetes or thyroid disorders, oral drugs such as decongestants could pose a risk of unfavorable drug interactions and may cause an adverse reaction. It would, therefore, be highly desirable to deliver relief from specific nasal symptoms via compositions without the need for such pharmaceutical actives.

Nasal delivery of therapeutic agents has been well known for a number of years. See, for example, U.S. Patent 4,749,700 to Wenig, issued June 7, 1988, U.S. Patent 4,778,810 to Wenig, et al., issued October 18, 1988 and U.S. Patent 4,729,997 to Wenig issued March 8, 1988. Nasal saline sprays have been used to moisturize nasal passages and to dissolve build-up in the nasal mucosa; however, saline solutions alone have not proved satisfactory for relief of nasal congestion. Menthol has been administered orally from lozenges and the like as well as delivered to the nasal mucosa from an inhaler containing a wick and no other excipients, see, for example, Clinical Otolaryngology, 1988, vol. 13, pps. 25-29. Yet menthol delivered in such a manner has not been found to provide a sufficient level of relief.

It has been discovered that topical aromatic decongestant pharmaceutical compositions containing one or more volatile aromatic compounds selected from the group consisting of menthol, camphor and eucalyptus oil and derivatives thereof and mixtures thereof along with a pharmaceutically-acceptable saline solution carrier provides the user with improved actual and/or perceived relief from nasal symptoms such as congestion and the like without the need for pharmaceutical actives such as oxymetazoline. In addition, such compositions will not cause drowsiness or other side effects attendant with oral decongestants.

It is therefore an object of the present invention to provide topical aromatic decongestant compositions which provide treatment for nasal symptoms resulting from, for example, colds, flu, allergy and sinus. It is a further object of the present invention to provide compositions which provide the user with improved actual and/or perceived relief from nasal symptoms such as congestion and the like without the need for pharmaceutical actives. It is still a further object of the present invention to provide compositions which minimize the likelihood of adverse drug interactions and further which provide for proper medication management.

SUMMARY OF THE INVENTION

The present invention relates to topical aromatic decongestant compositions for nasal administration consisting essentially of:

- (a) from about 0.001% to about 0.3% of one or more volatile aromatic compounds selected from the group consisting of menthol, camphor and eucalyptus oil and derivatives thereof and mixtures thereof;
- (b) from about 0.01% to about 99.99% of a pharmaceutically-acceptable aqueous saline solution carrier.

The present invention also relates to a method for treatment of nasal symptoms comprising administering a safe and effective amount of these topical aromatic releasing decongestant compositions. By nasal symptoms is meant congestion, dryness, irritation, runny nose, blockage and the like.

All levels and ratios are by weight of the total composition, unless otherwise indicated.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the present invention contain the essential components as well as various optional components as indicated below.

More specifically, the compositions of the instant invention are for nasal administration and contain a therapeutically effective amount of the selected aromatic agent or agents. They are preferably provided as isotonic aqueous solutions, suspensions or viscous compositions which may be buffered to a selected pH.

Aromatic Component.

The first essential component of the present invention is an aromatic component. This aromatic component comprises from about 0.001% to about 1%, preferably from about 0.1% to about 0.5% and most preferably from about 0.1% to about 0.3% of one or more volatile aromatic compounds selected from the group consisting of menthol, camphor and eucalyptus oil and derivatives thereof and mixtures thereof. These aromatic components are more fully described in 53 Federal Register 30561, August 12, 1988, incorporated by reference herein.

Pharmaceutically-Acceptable Saline Nasal Carrier.

The second essential component of the present invention is a pharmaceutically-acceptable aqueous saline solution carrier. These solutions which generally contain sodium chloride as the salt are fully described in Remington's Pharmaceutical Sciences, 17th edition (1985) p. 835, which is hereby incorporated by reference herein. The salt is present in the solution at a level of about 0.01% to about 2%, preferably from about 0.5% to about 1.0% and most preferably from about 0.5% to about 0.75%.

Any of the aromatics identified above can be conveniently administered nasally to warm-blooded animals to elicit the desired therapeutic response by formulating it into a nasal dosage form, together with a nontoxic pharmaceutically-acceptable nasal carrier. As indicated earlier, the aromatic can be employed in compositions of the present invention. Suitable nontoxic pharmaceutically-acceptable nasal carriers are known to those skilled in the art and are also fully disclosed in Remington's Pharmaceutical Sciences, 17th edition, 1985, which is hereby incorporated by reference herein. Obviously, the choice of suitable carrier forms will depend on the exact nature of the particular nasal dosage form required, e.g., whether the drug is to be formulated into a nasal solution (for use as drops or as a spray), a nasal suspension, a nasal ointment, a nasal gel or another nasal form. Preferred nasal dosage forms are solutions, suspensions and gels, which normally contain sodium chloride in a major amount of water (preferable purified water) in addition to the aromatic. Minor amounts of other ingredients such as pH adjusters (e.g., a base such as NaOH), emulsifiers or dispersing agents, buffering

agents, preservatives, wetting agents and jelling agents (e.g., methylcellulose) may also be present.

Most preferably, the nasal composition is isotonic, i.e., it has the same osmotic pressure as blood and lacrimal fluid. If
5 desired, sustained release nasal compositions, e.g., sustained release gels can be conveniently employed.

Those skilled in the art will be aware that a therapeutically effective amount of a particular agent will vary with the particular agent, the age, size, weight and general physical condition of the
10 patient; however, the advantage of the present invention over conventional topical nasal decongestants containing pharmaceutical actives is that the compositions of the present invention can be used as frequently as desired.

As a practical matter the selected therapeutic compositions
15 will normally be prepared in dosage unit forms to contain therapeutically effective amounts of the selected aromatic. In specific instances fractions of the dosage units or multiple dosage units will be employed. Typically dosage units may be prepared to deliver from about 0.01 mg to about 5 mg, preferably from about 0.5
20 mg to about 1 mg and most preferably from about 0.1 mg to about 0.5 mg of aromatic agent per dose (e.g., 50 mg to about 150 mg of spray). A typical dose contains two to three sprays per nostril.

The desired isotonicity of the compositions of this invention may be accomplished using, for example, the sodium chloride already
25 present, or other pharmaceutically-acceptable agents such as dextrose, boric acid, sodium tartrate, sodium phosphate, potassium phosphate, propylene glycol or other inorganic or organic solutes. Sodium chloride is preferred particularly for buffers containing sodium ions.

30 Viscosity of the compositions may be maintained at the selected level using a pharmaceutically-acceptable thickening agent. Methyl cellulose is preferred because it is readily and economically available and is easy to work with. Other suitable thickening agents include, for example, xanthan gum, carboxymethyl cellulose,
35 hydroxypropyl cellulose, carbomer, and the like. The preferred concentration of the thickener will depend upon the agent selected. The important point is to use an amount which will achieve the

selected viscosity. Viscous compositions are normally prepared from solutions by the addition of such thickening agents.

Preferred compositions within the scope of this invention will contain from about 0.01% to about 5% of a humectant to inhibit drying of the mucous membrane and to prevent irritation. Any of a variety of pharmaceutically-acceptable humectants can be employed including, for example sorbitol, propylene glycol or glycerol. As with the thickeners, the concentration will vary with the selected agent, although the presence or absence of these agents, or their concentration is not an essential feature of the invention.

Enhanced absorption across the nasal membrane can be accomplished employing a therapeutically acceptable surfactant. Typically useful surfactants for these therapeutic compositions include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Tween 80, Polyoxyl 40 Stearate, Polyoxylethylene 50 Stearate and Octoxynol, as well as Oxyethylated tertiary octyl phenol formaldehyde polymer (available from Sterling Organics as tyloxapol). The usual concentration is from 0.5% to 10% based on the total weight.

A pharmaceutically-acceptable preservative is generally employed to increase the shelf life of the compositions. Benzyl alcohol is suitable, although a variety of preservatives including, for example, Parabens, thimerosal, chlorobutanol, phenylmercuric acetate or benzalkonium chloride may also be employed. The most preferred preservative system for use herein comprises a combination of benzalkonium chloride, chlorhexidine gluconate and disodium EDTA. A suitable concentration of the preservative will be from 0.001% to 2% based on the total weight, although there may be appreciable variation depending upon the agent selected.

Aromatics. Various other non-active aromatic components (e.g., aldehydes and esters) may also be used. These aromatics include, for example, benzaldehyde (cherry, almond); citral (lemon, lime); neral; decanal (orange, lemon); aldehyde C-8, aldehyde C-9 and aldehyde C-12 (citrus fruits); tolyl aldehyde (cherry, almond); 2,6-dimethyl-octanal (green fruit); and 2-dodecenal (citrus, mandarin). Mixtures of these aromatics can also be used.

Other Optional Components. A variety of additional ingredients may be added to the emulsion compositions of the present invention. These additional ingredients include various polymers for aiding the film-forming properties and substantivity of the formulation, preservatives for maintaining the antimicrobial integrity of the compositions, antioxidants, and agents suitable for aesthetic purposes such as fragrances, pigments, and colorings.

The compositions can also contain low levels of insoluble ingredients added, for example for visual effect purposes, e.g. thermochromic liquid crystalline materials such as the microencapsulated cholesteryl esters and chiral nematic (nonsterol) based chemicals such as the (2-methylbutyl) phenyl 4-alkyl(oxy)benzoates available from Hallcrest, Glenview, Illinois 60025, U.S.A.

The pH of the compositions is preferably from about 5 to about 9, more preferably from about 5.5 to about 7.

Preferably the composition is applied to the nasal mucosa via topical application of a safe and effective amount of the composition to treat nasal symptoms. The amount of aromatic agent and frequency of topical application to the nasal mucosa can vary widely, depending upon personal needs, but it is suggested as an example that topical application range from about once per day to about twenty times daily, preferably from about twice per day to about ten times daily with use of from about 0.01 mg to about 5 mg of aromatic agent per dose (e.g., 50 mg to about 150 mg of spray).

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

Ingredients are identified by chemical or CTFA name.

EXAMPLE I

A topical nasal aromatic composition is prepared by combining the following components utilizing conventional mixing techniques.

5	<u>Ingredients</u>	<u>W/W%</u>
	Tyloxapol	0.70
	Sodium Phosphate	0.10
	Potassium Phosphate	0.35
	Sodium Chloride	0.65
10	Eucalyptol	0.05
	Camphor, Synthetic	0.03
	Menthol, Natural/Synthetic	0.10
	Disodium EDTA	0.01
	Benzalkonium Chloride (50%)	0.04
15	Chlorhexidine Gluconate (20%)	0.27
	Water, Purified QS.	100.00

20 Tyloxapol and water are added to an appropriately sized vessel and completely mixed under low heat. Ingredients are added one at a time with mixing, allowing each to dissolve before adding the next. The aromatics are blended together in a separate premix before being added to the batch. A separate premix is also made for chlorhexidine gluconate. After all ingredients have been added, purified water is used to bring the batch to the appropriate weight.

25 Administration of approximately 0.5 grams of the composition is used for topical nasal application to provide relief from nasal symptoms.

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EXAMPLE II

A topical nasal aromatic composition is prepared by combining the following components utilizing conventional mixing techniques.

	<u>Ingredients</u>	<u>W/W%</u>
5	Pluronic L-44	2.50
	Sodium Phosphate	0.10
	Potassium Phosphate	0.35
	Sodium Chloride	0.65
	Camphor	0.03
10	Menthol	0.10
	Disodium EDTA	0.01
	Benzalkonium Chloride (50%)	0.04
	Chlorhexidine Gluconate (20%)	0.27
	Water, Purified QS.	100.00

15 Administration of approximately 0.5 grams of the composition is used for topical nasal application to provide relief from nasal symptoms.

EXAMPLE III

20 A topical nasal aromatic composition is prepared by combining the following components utilizing conventional mixing techniques.

	<u>Ingredients</u>	<u>W/W%</u>
	Tyloxapol	0.70
	Sodium Phosphate	0.10
	Potassium Phosphate	0.35
25	Sodium Chloride	0.65
	Eucalyptol	0.05
	Camphor	0.03
	Menthol	0.10
	Parabens	0.30
30	Water, Purified QS.	100.00

Administration of approximately 0.5 grams of the composition is used for topical nasal application to provide relief from nasal symptoms.

EXAMPLE IV

A topical nasal aromatic composition is prepared by combining the following components utilizing conventional mixing techniques.

	<u>Ingredients</u>	<u>W/W%</u>
5	Tyloxapol	0.70
	Sodium Phosphate	0.10
	Potassium Phosphate	0.35
	Sodium Chloride	0.65
	Eucalyptol	0.05
10	Menthol	0.10
	Benzalkonium Chloride	0.20
	Water, Purified QS.	100.00

Administration of approximately 0.5 grams of the composition is used for topical nasal application to provide relief from nasal symptoms.

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CLAIMS:

1. A topical aromatic decongestant composition for nasal administration consisting essentially of:
 - (a) from 0.001% to 0.3% of one or more volatile aromatic compounds selected from the group consisting of menthol, camphor and eucalyptus oil and derivatives and mixtures thereof;
 - (b) from 0.01% to 99.99% of a pharmaceutically-acceptable aqueous saline solution carrier.
2. A topical aromatic decongestant composition according to Claim 1 wherein said aromatic compound is menthol and derivatives thereof.
3. A topical aromatic decongestant composition according to Claim 2 wherein the pharmaceutically-acceptable aqueous saline solution carrier is an isotonic aqueous buffer with a pH of from 3 to 7.
4. A topical aromatic decongestant composition according to any of the preceding claims wherein the pharmaceutically-acceptable aqueous saline solution carrier comprises from 0.01% to 2% salt, preferably sodium chloride.
5. A topical aromatic releasing composition according to any of the preceding claims which further comprises from 0.5% to 10% of a surfactant.
6. A topical aromatic releasing composition according to any of the preceding claims wherein said surfactant is selected from the group consisting of polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides Oxyethylated tertiary octyl phenol formaldehyde polymer.

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7. A topical aromatic releasing composition according to any of the preceding claims which further comprises from 0.01% to 5% of a humectant.
- 5 8. A topical aromatic decongestant composition according to any of the preceding claims wherein the carrier contains from 0.01% to 5% of a therapeutically acceptable thickening agent.

INTERNATIONAL SEARCH REPORT

PCT/US 93/05619

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 A61K9/00																	
BEST AVAILABLE COPY																	
II. FIELDS SEARCHED <div style="text-align: center; margin-top: 10px;">Minimum Documentation Searched⁷</div> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 25%; padding: 5px;">Classification System</td> <td style="padding: 5px;">Classification Symbols</td> </tr> <tr> <td style="padding: 5px;">Int.Cl. 5</td> <td style="padding: 5px;">A61K</td> </tr> </table> <div style="text-align: center; margin-top: 10px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched⁸</div>			Classification System	Classification Symbols	Int.Cl. 5	A61K											
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III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; padding: 5px;">Category ¹⁰</th> <th style="width: 70%; padding: 5px;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%; padding: 5px;">Relevant to Claim No.¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;"> EP,A,0 454 617 (WARNER-LAMBERT COMPANY) 30 October 1991 see page 5, line 10 - page 6, line 20 --- </td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-7</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;"> DE,A,3 818 094 (MEDICHEMIE AG) 20 July 1989 see page 3, line 63 - page 4, line 14 see examples 1,4 --- </td> <td style="text-align: center; vertical-align: top; padding: 5px;">1,4-8</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;"> US,A,2 156 254 (LESSEL L. MANCHEY) 29 October 1937 see column 1, line 1 - line 3 see column 2, line 53 - column 3, line 15 --- </td> <td style="text-align: center; vertical-align: top; padding: 5px;">1,2,4,8</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;"> FR,M,6 548 (HARLEY STREET NOMINEES LIMITED) 16 December 1968 see page 1, left column, line 1 - right column, line 7 ----- </td> <td style="text-align: center; vertical-align: top; padding: 5px;">1</td> </tr> </tbody> </table>			Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	EP,A,0 454 617 (WARNER-LAMBERT COMPANY) 30 October 1991 see page 5, line 10 - page 6, line 20 ---	1-7	X	DE,A,3 818 094 (MEDICHEMIE AG) 20 July 1989 see page 3, line 63 - page 4, line 14 see examples 1,4 ---	1,4-8	X	US,A,2 156 254 (LESSEL L. MANCHEY) 29 October 1937 see column 1, line 1 - line 3 see column 2, line 53 - column 3, line 15 ---	1,2,4,8	X	FR,M,6 548 (HARLEY STREET NOMINEES LIMITED) 16 December 1968 see page 1, left column, line 1 - right column, line 7 -----	1
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>																	
IV. CERTIFICATION <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;"> Date of the Actual Completion of the International Search <div style="text-align: center; font-weight: bold; font-size: 1.1em;">11 AUGUST 1993</div> </td> <td style="width: 50%; padding: 5px;"> Date of Mailing of this International Search Report <div style="text-align: center; font-weight: bold; font-size: 1.5em;">20.8.93</div> </td> </tr> <tr> <td style="padding: 5px;"> International Searching Authority <div style="text-align: center; font-weight: bold;">EUROPEAN PATENT OFFICE</div> </td> <td style="padding: 5px;"> Signature of Authorized Officer <div style="text-align: center; font-weight: bold;">VENTURA AMAT A.</div> </td> </tr> </table>			Date of the Actual Completion of the International Search <div style="text-align: center; font-weight: bold; font-size: 1.1em;">11 AUGUST 1993</div>	Date of Mailing of this International Search Report <div style="text-align: center; font-weight: bold; font-size: 1.5em;">20.8.93</div>	International Searching Authority <div style="text-align: center; font-weight: bold;">EUROPEAN PATENT OFFICE</div>	Signature of Authorized Officer <div style="text-align: center; font-weight: bold;">VENTURA AMAT A.</div>											
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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9305619
SA 75778

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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11/08/93

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